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(57) Abstract

The present invention provides a method for preventing or treating Central Nervous System (CNS) seizures comprising the administration of certain cis-N-(2-aminocyclohexyl)benzamides. The present invention also provides novel benzamides useful as CNS anti-seizure drugs.

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CIS-N-(2-AMINOCYCLOHEXYL)BENZAMIDE AND THEIR ENANTIOMERS AS ANTICONVULSANTS

Background of the Invention

The present invention provides a new use for some known benzamide compounds. More particularly, the present invention provides a method of treating or preventing Central Nervous System (CNS seizures), e.g., grand mal seizures, by the administration of certain cis-N-(2-aminocyclohexyl) benzamides. The present invention also provides novel cis-N-(aminocyclohexyl) benzamide compounds that are useful as CNS anti-seizure drugs in valuable warm blooded animals, including humans.

Information Disclosure

Certain benzamides are well-known. U.S. Patent No. 4,098,904 discloses some N-(2-aminocycloaliphatic) benzamide compounds, e.g., N-methyl-N-[2-(1-pyrrolidinyl) cyclohexyl]-3,4-dichlorobenzamide and N-methyl-N-[2-(N',N'-dimethylamino) cyclohexyl]-4-bromobenzamide, and salts and hydrates thereof as analgesic drug compounds.

U.S. Patent No. 4,145,435 discloses 2-aminocycloaliphatic alkanoyl amide compounds, e.g., N-methyl-N-[2-(N',N'-dimethylamino)cyclohexyl]-2-(4-bromophenyl) acetamide and their pharmaceutically acceptable salts as analgesic compounds.

U.S. Patent 4,215,114 discloses various methylamino-cyclohexyl-benzamide compounds useful as potent analgesics. In particular, a non-salt form of N-methyl-N-(2-(N'-methylamino)cyclohexyl)-3,4-dichlorobenzamide is specified; however, this is one among a large list of compounds not indicated to be useful for controlling or treating seizures.

U.S. Patent No. 4,801,604 discloses certain cis-N-(2-amino-cycloaliphatic) benzamides, e.g., cis-3,4-dichloro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzamides and salts thereof as anticonvulsants with little or no analgesic properties.

U.S. Patent 4,359,476 discloses N-[2-amino (oxy or thio group) substituted-cycloaliphatic]phenylacetamide and benzamide compounds which have analgesic activity. Wolf. T., et al, (1984), J. Or. Chem. 49:3305-3310 discloses 2-(0-chlorophenyl)-2-benzoylmethylamino)cyclohexanone. Certain oxazolidine rings are disclosed in Bernardi, L., et al, (1968), Gazz. Chim. Ital. 98(7):836-84). Burak, K., et al, (1985), Il Farmaco-Ed. Sc. 40(4):285-98 discloses aryl analogs of 2-0-chlorophenyl-2-methylaminocyclohexane-1-one hydrochloride which are useful as an anesthetic. None of the references cited above disclose that the compounds of the instant invention are useful as anticonvulsants.

It has been disclosed that after oral administration of U54494A (cis-3,4-dichloro-N-[2-(1-pyrrolidinyl)cyclohexyl]-benzamide and its enantiomers generate active metabolites in mice. See e.g. Von Voigtlander, P.F., et al. (1989), "Relationship of Anticonvulsant Activity to Brain Concentrations of the Chiral Anticonvulsant U-54494A", Drug Dev. Res. 18:205-216. However,

that publication is after the present invention was made and less than one year prior to the date of this application.

Summary of the Invention

The present invention provides novel monohydrochloride salt compounds:

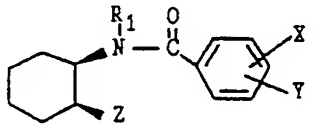
cis-N-(2-aminocyclohexyl)-3,4-dichlorobenzamide monohydrochloride and its enantiomers;

cis-N-[2-(methylamino)cyclohexyl]-3,4-dichlorobenzamide monohydrochloride and its enantiomers;

cis-N-(2-aminocyclohexyl)-3,4-dichloro-N-methyl-benzamide monohydrochloride and its enantiomers; and

cis-N-[2-(methylamino)cyclohexyl]-3,4-dichloro-N-methylbenzamide monohydrochloride and its enantiomers.

The present invention also provides novel methods of using the compounds of formula I:



I

wherein Z = NH_2 or $NHCH_3$ if ⎯ is a single bond or Z = O if ⎯ is a double bond;

wherein R_1 is H or C_{1-C3} alkyl;

wherein X and Y are the same or different and are hydrogen, F, Cl, or Br or a trifluoromethyl group; its enantiomers and pharmacologically acceptable salts thereof.

By the term "salt" we mean a compound that is prepared by reacting a formula I free base with a stoichiometric amount of an acid, e.g., hydrogen chloride, hydrogen bromide, hydrogen iodide, sulfuric acid, phosphoric acid, acetic acid, lactic acid, citric acid, succinic acid, benzoic acid, salicylic acid, pamoic acid, cyclohexane-sulfonic acid, methanesulfonic acid, naphthalenesulfonic acid, p-toluene-sulfonic acid, maleic, fumaric acid, oxalic acid.

By the term "C_1-C_3 alkyl", we mean an alkyl of one to three carbon atoms, inclusive of methyl, ethyl, propyl and isomeric forms thereof.

By treatment is meant the amelioration or total avoidance of the CNS disorder as described herein. By prevention is meant the avoidance of a currently recognized disease state, as described herein, in a patient evidencing a CNS disorder.

Detailed Description of the Invention

The present invention provides a method of treating or preventing certain CNS seizures in a patient susceptible to or experiencing said seizure comprising the systemic administration of certain cis-aminocyclohexyl-benzamide compounds or a pharmacologically acceptable salt thereof.

The present invention also provides novel benzamide compounds which are useful as anticonvulsants.

We discovered that the compounds of the instant invention are metabolites of cis-3,4-dichloro-N-methyl-N-[2-(1-pyrrolidinyl) cyclohexyl]-benzamide in mice. Surprisingly and unexpectedly, the compounds of the present invention are more effective as anticonvulsants than cis-3,4-dichloro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-benzamide. The compounds of the instant invention are generated in only very small amounts from cis-3,4-dichloro-N-methyl-N-[2-1-(pyrrolidinyl)cyclohexyl]benzamide by humans. In contrast, cis-3,4-dichloro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl] benzamide is rapidly bioinactivated by primates, including man. Thus, the compounds of the instant invention will be useful in the treatment of grand mal and other seizure disorders in man as well as in commercially important and pet animals.

Generally, the cis-N-(2-aminocyclohexyl)benzamides can be prepared in the following way.

A solution of substituted benzoyl chloride (.1 mol) dissolved in dichloromethane (200 ml) is added drop by drop to a mechanically stirred heterogenous solution of cis-1,2-diaminocyclohexane (.11 mol) in dichloromethane (1500 ml) and aqueous sodium hydroxide (5M, 200 ml). The organic phase is separated and concentrated to a solid mixture which is dissolved in warm ethyl acetate and allowed to crystallize. The crystalline product is the bis-amide. The filtrate is concentrated to a residue which is flash chromatographed (silica gel, 1% methanol-chloroform) to give cis-N-(2-aminocyclohexyl)benzamide.

A solution of cis-N-(2-aminocyclohexyl)benzamide-N-methanol is treated with excess methanolic hydrochloric acid and the resulting precipitate is recrystallized from methanol and ether to give the monohydrochloride salt of the titled compound.

The compounds of this invention, while being anti-seizure drugs, e.g., anti-convulsant drugs at reasonable dosages, have little or no analgesic activity and will not show some of the side effects of other anticonvulsants, e.g., hyperplasia of the gums, cerebellar degeneration, gastric distress and serious skin rashes. The anticonvulsant potency of these cis-aminocyclohexyl-benzamide compounds in standard laboratory animal tests indicate that these compounds are useful for preventing or treating CNS seizure disorders in warm-blooded animals such as cats, dogs, horses, as well as humans at dosage ranges of approximately 10 to 1000 mg/kg of body weight/day via the oral or parenteral routes until the seizure threat or attack subsides. The determination of specific dose ranges will vary with type, age, weight, sex and physical condition of the patient. It is within the skill of the attending physician or veterinarian to determine the specific dose range.

This invention also relates to compositions containing one of the compounds of the instant invention as an active ingredient in a pharmaceutical carrier. The compositions are useful in pharmaceutical dosage unit forms for systemic administration (oral, rectal, parenteral, including intravenous, intramuscular and intra-arterial administration form) for treating warm-blooded animal

patients, cats, dogs. horses and other commercially valuable animals and human patients suspected of being susceptible to or to stop CNS seizures. such as convulsions, grand mal, petit mal and other seizure disorders. The term "dosage unit form" as used herein refers to physically discrete units suitable as unitary dosages for mammalian subjects, each unit containing a predetermined quantity of the essential active ingredient compounds of this invention calculated to produce the desired effect in combination with the required pharmaceutical means which adapt the said ingredient for topical or systemic administration. The specifications for the novel dosage unit forms of the invention are indicated by and directly dependent on the physical characteristics of the essential active material for beneficial effects in humans and animals. Examples of suitable dosage unit forms in accordance with this invention are tablets, capsules, orally administered liquid preparations in suitable liquid vehicles for intramuscular and intravenous administration, suppositories and sterile clay preparations for the extemporaneous preparation of sterile injectable preparations in a suitable liquid vehicle. Suitable solid diluents are known in the art, e.g., starch, sucrose, lactose, kaolin, dicalcium phosphate, gelatin, acacia, corn syrup, corn starch, and talc.

The pharmaceutical dosage unit forms are prepared in accordance with the preceding general description to provide from about 1.0 to about 100 mg of the essential active ingredient per dosage unit form. The amount of the essential active ingredient provided in the pharmaceutical dosage unit forms is that amount sufficient to obtain a reduction in the CNS seizure effects and a return to more normal CNS stability or to prevent the occurrence of CNS seizures in a patient who is suspected to be subject to such seizure. Expressed otherwise, an amount of the essential active ingredient is provided to a recipient within a range of from about 0.1 mg per kg to about 100 mg per kg of body weight of the recipient. Preferred dosages for most applications are 1.0 to 10.0 mg, per kg of body weight.

The useful dosage unit forms of these compounds in pharmaceutical formulations is preferably adapted for oral administration to obtain anticonvulsant effects comprising an effective, nontoxic amount of the compound as described herein or as its pharmalogically acceptable salt. Further, the invention relates to methods of obtaining such CNS anti-seizure effects in mammals, e.g., humans and valuable warm-blooded animals such as dogs, cats, horses and other commercially valuable animals by administering systemically to the mammals pharmaceutical dosage unit forms, as described herein, supplying an effective, nontoxic amount for anticonvulsant effects. However, the compounds are less active when given intracerebroventricularly.

These specific cis-aminocyclohexyl benzamides have an advantage, to a greater or lesser extent, depending upon the particular compound, of having significant CNS anti-seizure properties, while having little or no significant analgesic activity. This combination of properties should prove beneficial and advantageous where the doctor would prefer to treat the patient for the single CNS seizure disorder without the need to worry about any significant analgesic side effects. Cis-N-(2-

aminocyclohexyl)-3,4-dichlorobenzamide monohydrochloride is the preferred compound. The most preferred compound is cis-N-[2-(methylamino)cyclohexyl]-3,4-dichlorobenzamide monohydrochloride.

The present invention is seen more fully by the examples given below.

Example 1 Cis-N-(2-aminocyclohexyl)-3,4-dichlorobenzamide monohydrochloride

A solution of 3,4-dichlorobenzoyl chloride (20.9 g) in dichloromethane (200 ml) is added dropwise at ambient temperature to a mechanically stirred heterogenous solution of cis-1,2-diaminocyclohexane (12.4 g) in dichloromethane (1500 ml) and aqueous sodium hydroxide solution (5 M, 200 ml). The addition takes 3 hours. The organic phase is separated, dried (anhydrous sodium sulfate (Na_2SO_4)), and concentrated in vacuo to a solid mixture.

The solid mixture is dissolved in hot ethyl acetate (EtOAc) and allowed to crystallize. The crystals are collected and washed with cold EtOAc and vacuumed dried at 20-25°C to give 19.0 g of a dimeric amide product.

Analysis for the dimeric amide product: Calc. C,52.20; H,3.94; N,6.10. Found: C,52.12; H,4.07; N,6.33.

The filtrate from the dimeric amide product is concentrated and flash chromatographed (silica gel 60, 230-400 mesh) eluting with 1% methanol-chloroform) to give 10.53 g of a colorless solid: PMR (MeOH-d_4) 1.45-1.80 ppm, 3.14, 4.10, 7.61, 7.75, 8.03.

A sample of the solid is treated with a solution of methanolic hydrochloric acid. The salt is recrystallized from methanol and ether to give cis-N-(2-aminocyclohexyl)-3,4-dichlorobenzamide monohydrochloride.

Anal. Calc. $C_{13}H_{16}N_2Cl_2O_1 \bullet HCl.0.5H_2O$: C,46.94; H,5.45; N,8.42; Cl,31.97. Found: C,47.06; H,5.57; N,8.30; Cl.

Example 2 3,4-dichloro-N-(2-oxocyclohexyl)benzamide

Jones reagent (8N, 1.5 ml) is added in three equal portions to a solution of starting amido-alcohol (1.35 g) in acetone (150 ml) at room temperature. The oxidation is complete after the last addition (tlc). Excess Jones reagent is quenched with isopropanol. The mixture is filtered with the aid of Celite and the filtrate is concentrated in vacuo. The solid is dissolved in dichloromethane and washed with water. The dried (Na_2SO_4) extract is concentrated in vacuo to a colorless solid which is recrystallized from ether-pet ether to give 1.16 g of colorless crystals of 3,4-dichloro-N-(2-oxocyclohexyl)-benzamide mp. 124-125°C.

Anal. Calc. for $C_{13}H_{12}N_1Cl_2O_2$: C,54.76; H,4.24; N,4.91; Cl,24.87. Found: C,54.37; H,4.84; N,4.89; Cl,25.17.

Example 3 Cis-N-(2-aminocyclohexyl)-3,4-dichloro-N-methyl-benzamidemonohydrochloride

Sodium cyanoborohydride (4.35 g) in methanol (50 ml) is added dropwise to a mixture of

amido-ketone (6.04 g), ammonium acetate (15.4 g), and 3A° molecular sieves (1/8 inch, 15 g) in methanol (130 ml) and THF (100 ml) under an argon atmosphere at room temperature. The mixture is stirred at ambient temperature for 20 hours. The mixture is filtered through celite and the cake is washed with methanol. The filtrate is concentrated to a small volume and diluted with 20% aqueous NaOH solution to a pH >10. The basic solution is extracted 3x with dichloromethane. The combined extracts is dried (Na_2SO_4) and concentrated in vacuo to ca. 6 g of oily mixture of products.

The oil is flash chromatographed on silica gel 60 (230-400 mesh) and eluted with 2.5% methanol-chloroform to give a non-polar component (ca. 2 g) of trans amido-alcohol:pmr ($CDCl_3$).

Further dilution provided 1.0 g of a dark staining product (rf=.6, (15% MeOH-$CHCl_3$, Iodine) as an oil: pmr ($CDCl_3$) .98-2.05, 2.75 and 3.20, 2.84 and 2.98, 4.1 and 4.3, 7.26-7.33, 7.47-7.59. A sample of the base is converted to the hydrochloric salt with ethereal HCl. The salt is recrystallized from a mixture of ethanol-acetone/ether to give cis-N-(2-aminocyclohexyl)-3,4-dichlorobenzamide.

Anal. Calc. for $C_{14}H_{18}N_2Cl_2O_1 \bullet HCl$: C,49.80; H,5.67; N,8.30; Cl,31.50. Found: C,49.30; H,5.82; N,8.36; Cl,30.85.

Alternatively, cis-N-(2-aminocyclohexyl)-3,4-dichloro benzamide can be prepared in the following way.

A solution of starting oxime (1.0 g) in methanolic ammonia (150 ml) is treated with one-half tablespoon of washed (3X with Ethanol) Raney Nickel (Aldrich) in a Parr bottle. The bottle is charged with H_2 gas (35psi). After 2 hours, the gas uptake will ceased. The catalyst is removed by filtration with the aid of Celite. The filtrate is concentrated in vacuo to give .9 g of an oil.

The oil is flashed chromatographed on silica gel 60 (230-400 mesh), and the product eluted from 2.5% MeOH-$CHCl_3$ mixture to give .45 g (48%) of the pure cis isomer. The pmr ($CDCl_3$) is identical to the spectrum of the free base of cis-N-aminocyclohexyl)-3,4-dichloro benzamide.

Further elution provided the more polar trans isomer (.2 g) which is inactive.

Example 4 Resolution procedure for cis-N-(2-aminocyclohexyl)-3,4-dichloro benzamide.

Solid 1,1-carbonyldiimidazole (1.83 g) is added in one portion to a solution of BOC-L-Phenylalanine (3.00 g) in THF (30 ml) at 0° under an Argon atmosphere. After the addition, the coolant is removed and the reaction is allowed to warm to 20-25°C for 1.5 hours. Recooled the reaction flask to 0°, a solution of cis-N-(2-aminocyclohexyl)-3,4-dichlorobenzamide (3.24) in THF (30 ml) is added dropwise within 10 min. The reaction flask is allowed to warm gradually to room temperature overnight. The reaction is diluted with aqueous saturated potassium carbonate solution and ethyl acetate. The phases are separated. The EtOAc phase is washed with water, dried (anhydrous sodium sulfate), and concentrated in vacuo to a mixture of diasteromeric amides.

The amide mixture is dissolved in hot EtOAc-EtOH solvent mixture and allowed to

crystallize at room temperature to give 1.7 g of a pure diasteromeric amide; mp. 224-225°C. This isomer is labeled A.

The mother liquor from A is concentrated and flash chromatographed (silica gel:230-400 mesh) with a 1% methanol-chloroform solution to give as a major component 2.59 g of diastereomer B (tlc:10% methanol in chloroform; visualized by UV and iodine vapor), rf=.81, contaminated with 16% of diastereomer A, rf=.85.

Trifluoroacetic acid (5 ml) is added to diastereomer A (1.6 g) at 20-25°C. After 30 min., the excess TFA is removed in vacuo, and the reaction is diluted with an ice-cold aqueous solution of 20% sodium hydroxide and dichloromethane. The phases are separated. The organic phase is reextracted with an ethyl acetate-toluene mixture. The combined extracts are dried (Na_2SO_4) and concentrated to give 1.2 g of deprotected amine A as an oil: rf=.70 (10% methanol in chloroform).

Trifluoroacetic acid (5 ml) is added to diastereomer B (2.59 g) at room temperature. After 30 min., the excess TFA is removed in vacuo, and the reaction is diluted with an ice-cold aqueous solution of 20% sodium hydroxide and dichloromethane. The phases are separated. The organic phase is reextracted with an ethyl acetate-toluene mixture. The combined extracts are dried (Na_2SO_4) and concentrated to give 1.7 g of deprotected amine which crystallized from EtOAc-Hexane to give B as a pure diastereomer: rf=.66 (10% methanol in chloroform).

Utilizing the method of K. E. Little, et al., (Tetrahedron Letters 28:521-522, 1987). phenylisothiocyanate (.134 g, 0.99 mmol) is added to a solution of A (.39 g, 0.90 mmol) in dichloromethane (3 ml). The reaction is kept in an oil bath at 50°C overnight. The solvent is removed in vacuo and the crude residue is flashed chromatographed (silica gel: mesh 230-400) with a 1% methanol-chloroform mixture to give ca. 0.5 g of isothiourea product as a foam.

The foam is dissolved in trifluoracetic acid (6 ml) and refluxed for 2 hours. The reaction is cooled, concentrated in vacuo to a residue, and then diluted with dichloromethane and aqueous 10% sodium hydroxide solution. The phases are separated. The dichloromethane extract is dried (Na_2SO_4) and concentrated to yellow oil which on standing crystallized. The nmr of this product is identical to the non-resolved amine.

The hydrochloric acid salt of the free base is prepared from ethereal hydrochloric acid and is recrystallized from an acetone-ether mixture to give enantiomer A: $[\alpha]_D = +2^o$ (MeOH, dcm, 0.8116 g).

Utilizing a similar procedure as above, enantiomer B (acetone-ether) is isolated: $[\alpha]_D = -2^o$ (MeOH, dcm, 1.0089 g).

Example 5 Cis-N-[2-(methylamino) cyclohexyl]-3,4-dichlorobenzamide monohydrochloride

Sodium cyanoborohydride (.15 g) is added to a suspension of 3,4-dichloro-N-(2-

oxocyclohexyl)-benzamide (.62 g), methylamine hydrochloride (.91 g), and potassium hydroxide (.51 g) in methanol (10 ml). The white suspension is stirred for 72 hours at 20-25°C. The mixture is diluted with ethyl acetate (100 ml) and 10% aqueous sodium hydroxide. The phases are separated. The organic phase is washed twice with water and then with a brine solution. The organic phase is dried over anhydrous sodium sulfate and concentrated in vacuo to an oily mixture. The mixture is chromatographed (silica gel, 240-400 mesh, eluant: 2% methanol-chloroform). Like fractions are combined and concentrated in vacuo. The product with rf=.48 (TLC:silica gel GF; develop with 15% methanol-chloroform, visualize with iodine) is treated with ethereal hydrochloric acid and the salt recrystallizes from methanol-ether to give colorless crystals of cis product.

Anal. Calc. for $C_{14}H_{18}N_2Cl_2O\bullet HCl$: C,49.80; H,5.67; N,8.70; Cl,31.50. Found: C,49.65; H,5.82; N,8.28; Cl,31.56.

Further elution provides the trans isomer which is inactive.

Example 6 Cis-N-2-(aminocyclohexyl) benzamide

In a manner similar to the preparation of cis-N-2-(aminocyclohexyl-3,4-dichlorobenzamide, cis-N-2-(aminocyclohexyl) benzamide is prepared from benzoyl chloride and cis-1,2-diamino-cyclohexane. The free base of the product is converted to the hydrochloride salt with ethereal hydrochloric acid and recrystallizes from ethanol-ether.

Anal. Calc. for $C_{13}H_{18}N_2O\bullet HCl$: C.61.29; H.7.52; N.10.99; Cl,13.92. Found: C,61.13; H,7.36; N,10.87; Cl,13.69.

Example 7 Cis-N-(2-aminocyclohexyl)-4-chlorobenzamide monohydrochloride

As in the above manner, cis-N-(2-aminocyclohexyl)-4-chlorobenzamide mono-hydrochloride is prepared from 4-chlorobenzoyl chloride.

Anal. Calc. for $C_{13}H_{17}N_2ClO\bullet HCl$: C,53.99; H,6.27; N,9.69; Cl,24.52. Found: C,53.80; H,6.50; N,9.97; Cl,24.07.

Example 8 Cis-N-(2-aminocyclohexyl)-4-bromobenzamide monohydro-chloride

As in the above manner, cis-N-(2-aminocyclohexyl)-4-bromobenzamide mono-hydrochloride is prepared from 4-bromobenzoyl chloride.

Anal. Calc. for $C_{13}H_{17}N_2BrO\bullet HCl$: C,46.80; H,5.44; N,8.40; Br,23.86; Cl,10.56. Found: C,46.83; H,5.45, N,8.22; Br,23.86; Cl,10.56.

Example 9 Cis-N-[2-(methylamino)cyclohexyl]-3,4-dichloro-N-methyl-benzamide monohydrochloride.

Titanium tetrachloride (.94g) in dichloromethane (10ml) is added dropwise to a solution of 2-[N-(tert-butyloxy)carbonyl]-N-methylamino]cyclohexanone (B.R. deCosta, et al., J. Med Chem., 32, 1996 (1989)), (2.04g) and N-methylbenzylamine(6.55g) in THF (40ml) at 0°C under an argon atmosphere. The mixture is stirred at room temperature for 20h. The precipitate is

filtered and washed with dichloromethane (3 x 50ml). The combined filtrates are concentrated to give a mixture of isomeric enamines which are contaminated with N-methylbenzylamine. No further purification is performed and this crude mixture is immediately utilized in the following reaction.

Crude enamine (8.9mmol) is hydrogenated and hydrogenolized with 10% palladium on carbon (1.5g) in ethyl acetate with H_2 (46psi). After the theoretical amount of hydrogen gas is consumed, the mixture is filtered and the catalyst is rinsed with ethyl acetate and ethanol. The combined filtrates are concentrated to give 1.73g of colorless oil. GC analysis: (HP1 column; flow rate 100ml/min, program run: 100^0/1min, then 20^0/min., final temp 250^0) rt=4.59min; NMR($CDCl_3$) partial δ 2.36ppm(N-CH_3), 2.90(N-CH_3), 3.9(N-CH).

A solution of 3,4-dichlorobenzoyl chloride (1.63g) in THF (10ml) is added dropwise to a solution of mono BOC protected diamine (1.7g) from the above, triethylamine (1.2ml) in THF (20ml) at 0^0C. under an argon atmosphere. The mixture is stirred at room temperature for 24h. The mixture is diluted with dichloromethane and aqueous saturated potassium carbonate solution and the phases are separated. The organic phase is washed with water, dried (Na_2SO_4), and then, concentrated to an oily mixture.

The mixture is flash chromatographed (silica gel, 10% ethyl acetate-hexane), the like fraction are combined and evaporated to give 1.52g of pure oily product; TLC: rf=.57(40%ethyl acetate-hexane).

Trifluoroacetic acid (3ml) is add to a solution of the starting BOC protected amine (1.05g) from the above in dichloromethane (15ml) at -78^0C. under an argon atmosphere. The mixture is stirred at room temperature for 2h. The solution is concentrated, and the residue is diluted with aqueous saturated potassium carbonate solution and dichloromethane. The phases are separated. The organic phase is dried and concentrated to oil which is immediately dissolved in ether and treated with ethereal hydrochloric acid. The precipitate salt is recrystallized from methanol-ether to give .64g of colorless crystals; mp. 168-170^0C.

Example 10 Anti-convulsants activity of cis-N-(2-aminocyclohexyl)-3,4-dichlorobenzamide monohydrochloride and cis-N-[2-(methylamino)cyclohexyl]-3,4-dichlorobenzamide monohydrochloride.

The anticonvulsant activity of these compounds were tested in Charles River CF-1 (18-22 gm) male mice. The mice are dosed either orally (PO), intravenously (IV) or intracerebroventricularly (ICV) with cis-N-(2-aminocyclohexyl)-3,4-dichlorobenzamide monohydrochloride,cis-3,4-dichloro-N-[2-(methylamino)cyclohexyl]benzamidemonohydrochloride, and cis,-3,4-dichloro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl] benzamide. The oral and intravenous doses of the compound ranged from 6.25 to 200 mg/kg, and the compound is dissolved in 0.9% saline and injected in a volume of 0.2 cc/20 gm. The intracerebroventricular doses ranged

from 6.25 to 200 ug/mouse and are administered in 10 ul of saline.

The mice used for the oral study had free access to water, but food is withdrawn 12 hours prior to oral injection. A curved gavage needle with a bulbus tip is used to administer drugs orally. Mice are intravenously injected via the tail vein using a 26 gauge needle. Intracerebroventricular injection into the left lateral ventricle is effected with a Hamilton 50 microliter syringe (model 705) with a fixed needle and provided with a stainless steel cuff to limit penetration. Anticonvulsant activity is assessed by determination of electroshock induced seizure thresholds. Generally 10 mice are utilized to establish the mA threshold for tonic seizures at each of the time intervals studied. The data is calculated as mA50 increase (threshold for treated mice-threshold of control mice) or as anticonvulsant ED_{50}'s based on the ability of the test compound to block seizures induced by a 100 mA 0.2 second stimulus.

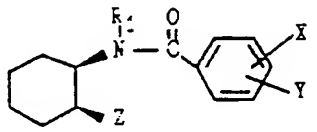
Dose response data determined at 30, 60, 120, 240, and 480 minutes after oral administration shows that cis-N-(2-aminocyclohexyl)-3-,4-dichlorobenzamide monohydrochloride and cis-N-[2-(methylamino)cyclohexyl]-3,4-dichlorobenzamide monohydrochloride are more potent than cis-4-dichloro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-benzamide. For IV administration, the results are reversed. Cis-N-(2-aminocyclohexyl)-3-4-dichlorobenzamide monohydrochloride and cis-3,4-dichloro-N-[2-(methylamino)cyclohexyl]benzamide monohydrochloride are comparatively ineffective when administered ICV.

Additional examples can be made following the procedures set forth in U.S. Patent No. 4.098.904 and 4,215,114 which is incorporated herein by reference.

CLAIMS

We claim:

1. The use of a compound of Formula I



I

wherein Z = NH_2 or $NHCH_3$ if — is a single bond or Z = 0 if — is a double bond;

wherein R_1 is H or C_1-C_3 alkyl;

wherein X and Y are the same or different and are hydrogen, F, Cl or Br or a trifluoromethyl group;

its enantiomers and pharmacologically acceptable salts thereof;

for the manufacture of a medicament for preventing or treating Central Nervous System seizures in a warm-blooded animal patient by administering to such patient an effective amount to prevent or reduce the effects of such seizure disorders.

2. The use according to Claim 1 wherein the compound of Formula I is selected from the group consisting of:

a. cis-N-(2-aminocyclohexyl)-3,4-dichloro-benzamide monohydrochloride, and its enantiomers;

b. N-(2-oxocyclohexyl)-3,4-dichlorobenzamide;

c. cis-N-[2-(methylamino)cyclohexyl]-3,4-dichloro-benzamidemonohydrochlorideand its enantiomers;

d. cis-N-(2-aminocyclohexyl)-3,4-dichloro-N-methyl-benzamide monohydrochloride;

e. cis-N-2-(aminocyclohexyl)benzamide;

f. cis-N-(2-aminocyclohexyl)-4-chlorobenzamide monohydrochloride;

g. cis-N-(2-aminocyclohexyl)-4-bromobenzamide monohydrochloride;

h. cis-N-[2-methylamino)cyclohexyl]-3,4-dichloro-N-methyl-benzamide monohydrochloride and its enantiomers; and

pharmacologically acceptable salts thereof.

3. A compound which is cis-N-(2-aminocyclohexyl)-3,4-dichlorobenzamide monohydrochloride and its enantiomers.

4. A compound which is cis-N-(2-methylamino)cyclohexyl]-3,4-dichlorobenzamide-monohydrochloride and its enantiomers.

5. A compound which is cis-N-(2-aminocyclohexyl)-3,4-dichloro-N-methyl-benzamide monohydrochloride and its enantiomers.

6. A compound which is cis-N-[2-(methylamino)cyclohexyl]-3,4-dichloro-N-methyl-benzamide monohydrochloride and its enantiomers.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 91/05473

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 K 31/165 C 07 C 233/79

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	A 61 K C 07 C

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
X	US,A,4801604 (PHILIP F. VONVOIGTLANDER et al.) 31 January 1989, see abstract; columns 1,2; example 3; claims 1-6 (cited in the application)	1,2
A		3-6

X	Drug Development Research, volume 18, no. 3, 1989, Alan R. Liss Inc. (New York, US), P.F. VonVoigtlander et al.: "Relationship of anticonvulsant activity to brain concentrations of the chiral anticonvulsant U-54494a", pages 205-216, see abstract; introduction; pages 209,215, (cited in the application)	1,2

A		3-6
	--- -/-	

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
06-11-1991	09. 12. 91
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	[signature] ...SEN

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	US,A,4215114 (JACOB SZMUSZKOVICZ) 29 July 1980, see abstract; column 3; example 51 (h) (cited in the application) ---	3-6
P,X	Heterocycles, volume 31, no. 10, 1990, B.R. de Costa et al.: "A practical synthesis, optical resolution and determination of absolute configuration of enantiomerically pure 1S,2R-(+)- and 1R,2S-(-)-CIS-2-(1-pyrrolidinyl)cyclohexylamines: important precursors for a new class of sigma-receptor ligands and anticonvulsant drugs", pages 1837-1846, see page 1837 ---	1,2
A	-----	3-6

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9105473 SA 51025

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 25/11/91. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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US-A- 4215114	29-07-80	US-A- 4098904	04-07-78
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